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A novel inflammation indicator of acute stent thrombosis and in-hospital mortality in acute coronary syndrome: multiple inflammation index

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ABSTRACT

Aim: The inflammatory milieu plays a triggering role in the development of acute stent thrombosis (ST), which occurs as a catastrophic complication following percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS). This study aimed to investigate the prognostic role of multi-inflammatory index (MII), a powerful new marker of inflammation, in predicting of high SYNTAX score, acute ST and in-hospital mortality in patients with ACS undergoing PCI.

Material and Method: This retrospective study included 1488 consecutive patients with ACS undergoing PCI, and definitive ST was determined according to Academic Research Consortium criteria. Inflammation indices were calculated as follows: Systemic immune inflammation (SII)=neutrophil×platelet/lymphocyte ratio, CAR=CRP/albumin ratio, MII-1=platelet×CRP/lymphocyte ratio, MII-2=neutrophil×CRP/lymphocyte ratio, MII-3=SII×CRP.

Results: The incidence of acute ST was 3.6%. All inflammation indices was higher in the acute ST group and high SYNTAX score group. Multivariable regression analysis showed that MII-3 independent predictors of acute ST and high SYNTAX score. MII-3 exhibited better diagnostic performance than other inflammatory indices. The threshold value of MII-3 in predicting acute ST was >9084 (AUC=0.842, sensitivity=87.3%, specificity=%77.8) and patients with MII-3 >9084 had a 3.73-fold greater risk of mortality.

Conclusion: MII-3 is a stronger predictor of acute ST following PCI and it is associated with an increased risk of mortality. MII may be an essential prognostic screening tool for identifying high-risk patients prior to procedure.

Keywords: Acute coronary syndrome, inflammation, stent thrombosis, SYNTAX score

INTRODUCTION

In acute coronary syndrome (ACS), which is one of the leading causes of death globally, Percutaneous coronary stent implantation, known as primary percutaneous coronary intervention (PCI), is often used for treatment (1). Acute stent thrombosis (ST) is a catastrophic complication that occurs following PCI and is associated with myocardial infarction and sudden cardiac death (2). Its incidence is about 2.4% and has a mortality rate of up to 34% (2, 3). Acute ST processing may occur depending on the patient, lesion, stent characteristics, and efficacy of antiaggregant treatment. However, pre-procedural indicators are not well defined yet (2, 4).

Increasing evidence suggests that the inflammatory milieu plays a vital role in the development of acute ST (5, 6). This could potentially point to microvascular and molecular mechanisms involving ischemia, oxidative stress, endothelial damage, and innate immune cells (7, 8). Previous studies have reported that the systemic immune inflammation index (SII) derived from inflammatory immune cells is a superior predictor of cardiac events (9, 10). Recent studies in different diseases have suggested that multi-inflammatory indices (MII) obtained from the combination of inflammatory immune cells and C-reactive protein (CRP), an acute phase reactant, are a better prognostic indicator (11-13). However, the diagnostic performance of MII in cardiovascular disease or events has not been investigated yet.

This study aimed to investigate the prognostic role of MII in predicting high SYNergy between Percutaneous Coronary Intervention with TAXus and cardiac surgery (SYNTAX) score, acute ST and in-hospital mortality in patients with ACS undergoing PCI.

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MATERIAL AND METHOD

This retrospective study was performed on ST-segment elevation myocardial infarction (STEMI) patients who underwent primary PCI from a single-center Cardiology Clinic between January 2018 and January 2021. The study followed the revised Declaration of Helsinki (2013, Brazil) and all ethical procedures and was approved by the Ankara City Hospital Ethics Committee (Date: 30.11.2022, Decision No: E1-22-3056). The need for informed consent was waived under the approval of the Local Ethics Committee due to the retrospective design.

Patient Selection

2684 consecutive patients diagnosed with STEMI who underwent PCI were evaluated retrospectively. STEMI was defined following the fourth universal definition of MI (14) with management procedures being aligned with the latest guidelines of the European Society of Cardiology (15). Angiographic data were analyzed in the cardiac catheterization laboratory. At the operator's discretion, ticagrelor (180 mg) or prasugrel (60 mg) was loaded in addition to aspirin (300 mg). 1196 patients who did not meet the inclusion criteria were excluded. Exclusion criteria were a history of inflammatory disease or active inflammatory conditions, kidney or liver disease, autoimmune disease, cancer, history of anti-inflammatory or chronic corticosteroid or nephrotoxic drugs, heart valve disease, dilated cardiomyopathy, decompensated heart failure, previous revascularization history, oral anticoagulant use, persistent coronary dissection, undersized stent, attempt bifurcation, loading clopidogrel as antiaggregant, intraprocedural stent thrombosis, residual thrombus or stenosis >50%, no reflow during PCI (thrombolysis in myocardial infarction [TIMI] flow grade <3), pregnant or had delivered within the last 90 days, and missing data on clinical measurements. After the exclusion, 1488 patients were included in this study (**Figure 1**).

All patients' demographic, comorbid diseases and clinical data were obtained from the hospital's electronic information system and patient files.

Definitions

Acute ST was defined as ST occurring within the first 24 hours after percutaneous coronary stent implantation. Definitive ST was evaluated according to the following Academic Research Consortium criteria: (1) the Presence of a thrombus that originates from the stent or the segment 5 mm proximal or distal to the stent (occlusive or not), and (2) at least one of the following: Acute ischemic symptom onset at rest and/or new ischemic electrocardiogram changes suggestive of acute ischemia and/or typical increase and decrease in cardiac biomarkers. In repeated measurements, blood pressure >140/90 mmHg or antihypertensive drugs was defined as hypertension, and fasting plasma glucose (FPG) level ≥126 mg/dL or using antidiabetic drugs was defined as diabetes mellitus.

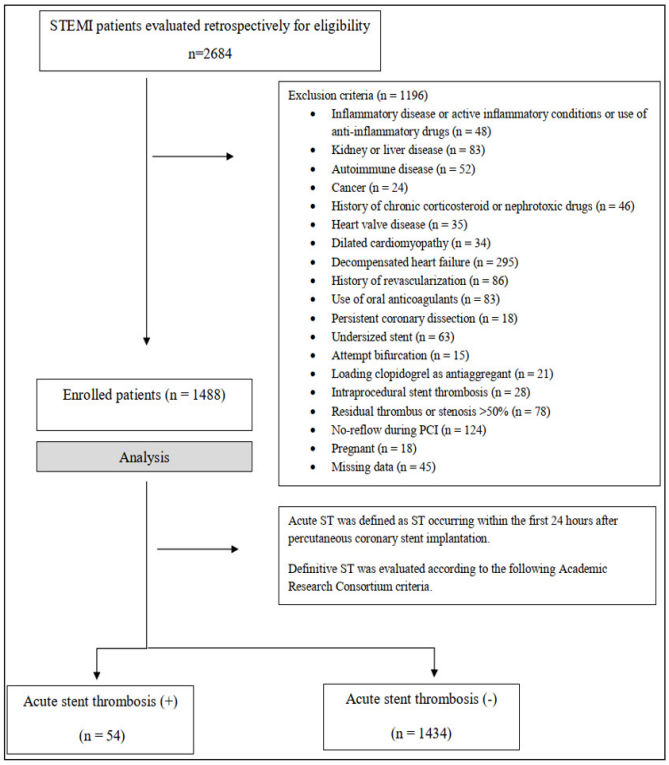
STEMI patients evaluated retrospectively for eligibility
n=2684
Exclusion criteria (n = 1196)
Inflammatory disease or active inflammatory conditions or use of anti-inflammatory drugs (n = 48)
Kidney or liver disease (n = 83)
Autoimmune disease (n = 52)
Cancer (n = 24)
History of chronic corticosteroid or nephrotoxic drugs (n = 46)
Heart valve disease (n = 35)
Dilated cardiomyopathy (n = 34)
Decompensated heart failure (n = 295)
History of revascularization (n = 86)
Use of oral anticoagulants (n = 83)
Persistent coronary dissection (n = 18)
Undersized stent (n = 63)
Attempt bifurcation (n = 15)
Loading clopidogrel as antiaggregant (n = 21)
Intraprocedural stent thrombosis (n = 28)
Residual thrombus or stenosis >50% (n = 78)
No-reflow during PCI (n = 124)
Pregnant (n = 18)
Missing data (n = 45)
Enrolled patients (n = 1488)
Analysis
Acute ST was defined as ST occurring within the first 24 hours after percutaneous coronary stent implantation.
Definitive ST was evaluated according to the following Academic Research Consortium criteria.
Acute stent thrombosis (+)
(n = 54)
Acute stent thrombosis (-)
(n = 1434)

Figure 1. Flow diagram of the cohort study

Laboratory Analysis

Blood samples were taken at the time of admission and during the follow-up and were measured using Beckman Coulter LH 780 (Mervue, Galway, Ireland). The levels of hemoglobin (photometrically), platelets (impedance method), CRP (immunoturbidimetric method), albumin (bromine cresol green method), triglycerides, and total cholesterol (enzymatic colorimetric method) and HDL (homogeneous enzymatic colorimetric method) were determined. Low-density lipoprotein (LDL) levels were calculated using the Friedewald formula. Inflammation indices were calculated as follows: PLR=platelet to lymphocyte ratio, NLR=neutrophil to lymphocyte ratio, SII=neutrophil count×platelet count/lymphocyte count, CAR=CRP to albumin ratio, MII-1=PLR×CRP, MII-2=NLR×CRP, MII-3=SII×CRP. Cardiac troponin I (cTnI) levels were measured intermittently up to the peak level using a Roche Diagnostics Cobas 8000 c502 analyzer (Roche Diagnostics, Indianapolis, IN, USA).

Coronary Angiography

Coronary arteries were visualized with the standard Judkins technique, and cine-angiographic images were recorded (AXIOM Artis, Siemens AG, Munich, Germany). At least two orthogonal plan images were

taken for each segment. Based on the baseline coronary angiograms, the SYNTAX score was calculated by two cardiologists blinded to the patients data. The SYNTAX score was evaluated for all lesions with a >50% diameter stenosis in a vessel greater than 1.5 mm according to the SYNTAX score calculator 2.1 (www.syntaxscore.org). Accordingly, all patients were divided into 2 groups as low (<23) and high (≥23) SYNTAX scores. In 200 randomly selected patients, the kappa (k) value was 0.94 at intra-observation reliability and 0.92 at interobserver reliability. Echocardiographic data were measured with a 2.5 MHz phased array transducer (Vingmed GE, Horten, Norway), and left ventricular ejection fraction (LVEF) was calculated using the modified Simpson's method.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). The normality distribution of numerical data was evaluated with the Kolmogorov-Smirnov test. Normally distributed variables were presented as mean±standard deviation, and non-normally distributed variables were presented as median (25^{th} and 75^{th} percentiles). For comparisons between groups, the Student T-test and Mann-Whitney U test were used according to normality distribution. Categorical variables were expressed as numbers and percentages, and comparisons between groups were evaluated with Chi-square and Fisher's Exact tests. Spearman's correlation analysis links inflammation indices and the SYNTAX score. Potential confounding factors for acute ST and high SYNTAX score were identified by multivariable regression analysis. Components of inflammatory indices were not included in the regression analysis due to multi-collinearity. A multivariate regression model (Model I) was constructed with potential confounding factors and SII and CAR inflammation indices but not MII. Next, a new multivariate regression model (Model II) was created in which MII-3 was included in Model I, but SII was omitted due to multi-collinearity. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of the inflammation indices to predict acute ST. $P < 0.05$ was considered statistically significant.

RESULTS

The mean age of 1488 patients included in the study was 58.4±11.2 years, the majority of them were male (75.2%), and the incidence of acute ST was 3.6%. The demographic and clinical characteristics of patients were reported in **Table 1**. Demographic findings did not differ between groups with and without acute ST ($p > 0.05$). Mean LVEF levels were lower in the acute ST group than without the acute ST group, while the median SYNTAX score and mean number of severely diseased vessels were higher ($p < 0.05$). NLR, PLR SII, CRP, CAR, and MII levels were higher in the acute ST group than without the acute ST group (**Table 1**).

Potential confounding factors associated with acute ST were determined as LVEF, stent length, number of SDV, SYNTAX score, cTnI, leukocytes, CRP, albumin and inflammatory indices. Model I regression analysis showed that SII (OR=1.10, $p < 0.001$) and CAR (OR=1.15, $p < 0.001$) were independent predictors of acute ST, while Model II regression analysis showed MII-3 (OR=1.06, $p < 0.001$). In both models, stent length, number of SDV, and SYNTAX score were common independent predictors of acute ST. However, Model II regression analysis improved the variance in explaining acute ST compared to Model 1 regression analysis (Nagelkerke R2=0.508 for Model II vs. Nagelkerke R2=0.415 for Model I) (**Table 2**).

Table 2. Independent predictors of acute stent thrombosis.

Variables	OR (95% CI)	p value
Univariable		
LVEF	0.97 (0.95-0.99)	0.045
Stent length	1.13 (1.07-1.21)	< 0.001
Multivessel disease	1.75 (1.01-3.04)	0.047
Number of SDV	2.30 (1.55-3.42)	< 0.001
SYNTAX score	1.09 (1.06-1.12)	< 0.001
cTnI	1.02 (1.01-1.03)	< 0.001
WBC	1.12 (1.04-1.19)	0.043
NLR	1.16 (1.08-1.25)	< 0.001
PLR	1.09 (1.06-1.12)	< 0.001
SII, $\times 10^2$	1.06 (1.03-1.10)	< 0.001
CAR	1.12 (1.06-1.18)	< 0.001
MII-1	1.08 (1.04-1.12)	< 0.001
MII-2, $\times 10^2$	1.03 (1.02-1.05)	< 0.001
MII-3, $\times 10^2$	1.05 (1.03-1.06)	< 0.001
Model I Multivariable		
Stent length	1.12 (1.06-1.20)	< 0.001
Number of SDV	2.26 (1.48-3.43)	< 0.001
SYNTAX score	1.06 (1.02-1.10)	0.006
SII, $\times 10^2$	1.10 (1.08-1.21)	< 0.001
CAR	1.15 (1.08-1.21)	< 0.001
	Nagelkerke R2=0.415, p<0.001	
Model II Multivariable		
Stent length	1.15 (1.08-1.22)	< 0.001
Number of SDV	2.27 (1.50-3.45)	< 0.001
SYNTAX score	1.05 (1.01-1.09)	< 0.001
MII-3, $\times 10^2$	1.06 (1.04-1.08)	< 0.001
	Nagelkerke R2=0.508, p<0.001	

Abbreviations: CAR, C-reactive protein to albumin ratio; CI, confidence interval, LVEF, left ventricular ejection fraction; MII, multi-inflammation index; NLR, neutrophil to lymphocyte ratio; OR, odds ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index; SDV, severely diseased vessels; SYNTAX, SYNergy between Percutaneous Coronary Intervention with TAXus and cardiac surgery; WBC, white blood cell.

Table 1. The demographic and clinical characteristics.

Variables	Study population n=1488	Acute ST (+) n=54	Acute ST (-)	p value
Age, years	58.4±11.2	58.6±9.4	58.4±11.3	0.901
Male gender, n (%)	1119 (75.2)	39 (72.2)	1080 (75.3)	0.630
Smoking, n (%)	577 (38.8)	26 (48.1)	551 (38.4)	0.157
Diabetes mellitus, n (%)	318 (21.4)	15 (27.8)	303 (21.1)	0.239
Hypertension, n (%)	640 (43.0)	25 (46.3)	615 (42.9)	0.675
LVEF, %	48.9±8.2	46.4±10.1	49.3±8.1	0.022
Stent length, mm	23.5±4.7	26.1±4.0	23.4±4.7	< 0.001
Stent diameter, mm	3.0±0.4	3.1±0.3	3.0±0.4	0.725
IRA, n (%)				
LAD	931 (62.6)	35 (64.8)	896 (62.5)	0.776
LCX	638 (42.9)	24 (44.4)	614 (42.8)	0.889
RCA	676 (45.4)	28 (51.9)	648 (45.2)	0.404
Multivessel disease, n (%)	683 (45.9)	32 (59.3)	651 (45.4)	0.044
Number of SDV	1.5±0.4	1.7±0.5	1.4±0.4	< 0.001
SYNTAX score	19.3 (13-25)	25.2 (21-32)	18.7 (13-24.5)	< 0.001
Tirofiban administration, n (%)	162 (10.8)	5 (9.3)	157 (10.9)	0.711
Medications, n(%)				
RAS blocker	511 (34.3)	19 (35.2)	492 (34.3)	0.885
Diuretics	330 (22.2)	11 (20.4)	319 (22.2)	0.868
β-blocker	383 (25.7)	12 (22.2)	371 (25.9)	0.636
CCB	330 (22.2)	13 (24.1)	317 (22.1)	0.739
Antiaggregant	409 (27.5)	13 (24.1)	396 (27.6)	0.643
Statin	365 (24.5)	12 (22.2)	353 (24.6)	0.750
OAD	302 (20.3)	14 (25.9)	288 (20.1)	0.302
cTnI, ng/mL	3.8 (1.6-21.8)	5.2 (2.8-20.7)	3.4 (1.7-8.9)	< 0.001
FBG, mg/dL	117.7±45.8	117.6±44.1	117.7±45.8	0.986
WBC, $10^3/mm^3$	8.6 (7.0-10.6)	9.1 (8.0-12.1)	8.6 (7.0-10.5)	0.032
Neutrophil, $10^3/mm^3$	5.3 (4.1-7.1)	6.6 (5.4-9.4)	5.3 (4.1-7)	< 0.001
Lymphocyte, $10^3/mm^3$	2.2 (1.7-2.8)	1.9 (1.6-2.4)	2.2 (1.7-2.8)	0.008
Platelet, $10^3/mm^3$	254.8±71.4	322.1±93.1	252.3±69.2	< 0.001
Hemoglobin, g/dL	14.2±1.5	14.1±1.6	14.2±1.5	0.922
Hematocrit, %	43.0±4.8	42.8±4.8	43.1±4.7	0.777
C-reactive protein, mg/L	7.2 (3.6-14.2)	14.3 (8.8-23)	7 (3.5-14)	< 0.001
Albumin, g/dL	3.9±0.4	3.7±0.6	3.9±0.4	0.006
Creatinine, mg/dL	0.9±0.3	0.9±0.2	0.9±0.3	0.483
Total cholesterol, mg/dL	192.4±78.5	192.7±45.5	192.4±79.5	0.983
LDL- cholesterol, mg/dL	121.9±38.3	119.8±41.8	122±38.2	0.670
HDL- cholesterol, mg/dL	40.2±9.7	41.6±9.2	40.1±9.8	0.240
Triglyceride, mg/dL	170 (120-231)	187.5 (127-255)	170 (120-230)	0.452
NLR	2.3 (1.7-3.5)	3.5 (2.6-5.3)	2.3 (1.7-3.5)	< 0.001
PLR	110.4 (83.9-151)	156.3 (112-215.9)	109.1 (83.5-150)	< 0.001
CAR	1.9 (0.9-3.8)	4 (3.2-6.7)	1.8 (0.9-3.7)	< 0.001
SII, $\times 10^2$	5.8 (4.0-9.6)	10.4 (6.5-17.0)	5.6 (3.9-9.2)	< 0.001
MII-1	17.8 (8.2-35.8)	47.1 (28.4-88.4)	17.1 (8.1-33.8)	< 0.001
MII-2, $\times 10^2$	8.5 (3.9-16.2)	22.0 (14.0-32.6)	8.3 (3.8-15.5)	< 0.001
MII-3, $\times 10^2$	45.0 (19.6-90.6)	145.0 (103.3-232.1)	42.4 (19.1-83.4)	< 0.001

Numerical variables were shown as mean±standard deviation or median (min-max). Categorical variables were shown as number (%). Abbreviations: CAR, C-reactive protein to albumin ratio; CCB, calcium channel blocker; cTnI, cardiac troponin-I; FBG, fasting plasma glucose; HDL, high density lipoprotein; IRA, infarct-related artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; MII, multi-inflammation index; NLR, neutrophil to lymphocyte ratio; OAD, oral antidiabetic drug; PLR, platelet to lymphocyte ratio; RAS, renin-angiotensin system; RCA, right coronary artery; SII, systemic immune-inflammation index; SDV, severely diseased vessels; SYNTAX, SYNergy between Percutaneous Coronary Intervention with TAXus and cardiac surgery; ST, stent thrombosis; WBC, white blood cell.

The diagnostic performance of inflammatory indices in predicting acute ST is shown in **Figure 1**. The threshold value of MII-3 in predicting acute ST was > 9084 with 87.3% sensitivity and 77.8% specificity and it exhibited better diagnostic performance than other inflammatory indices (**Figure 2A**). The rate of in-hospital mortality was 7.6% (n=113). The acute ST group had a higher in-hospital mortality rate than without acute ST group (24.1% vs. 7.0%, p < 0.001). The threshold value of MII-3 (> 9084) determined to predict acute ST was associated with a 3.73-fold increased risk of mortality (**Figure 2B**).

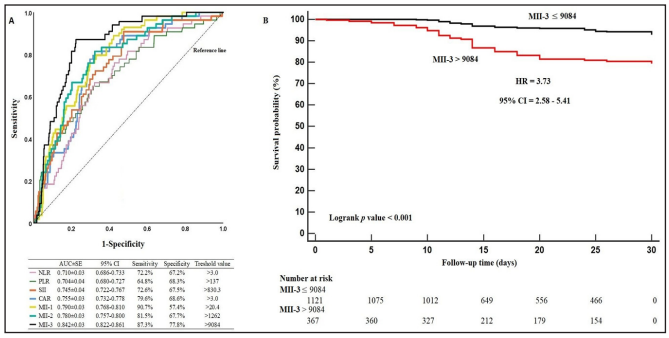

Figure 2. Diagnostic performance of inflammatory indices in predicting acute stent thrombosis (A) and in-hospital mortality risk according to the threshold value of MII-3 in predicting acute ST (B)

There was a positive correlation between the SYNTAX score and MII indices (r=0.405, p < 0.001 for MII-1; r=0.414, p < 0.001 for MII-2; r=0.426, p < 0.001 for MII-3) (**Figure 3**). Demographic and clinical findings associated with a high SYNTAX score are shown in Table (**Table 3**), and potential confounders for univariable regression analysis are presented in (**Table 4**). Model I regression analysis showed that SII (OR=1.05, p < 0.001) and CAR (OR=1.43, p < 0.001) were independent predictors of high SYNTAX score, while Model II regression analysis showed MII-3 (OR=1.10, p < 0.001). Model II explained the SYNTAX score with a higher variance than Model 1 (Nagelkerke R2=0.522 for Model II vs. Nagelkerke R2=0.433 for Model I).

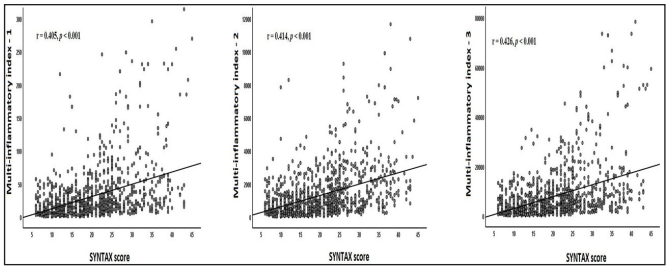

Figure 3. Correlation analysis between SYNTAX score and multi-inflammatory indices.

Table 3. Relationship between demographic and clinical characteristics and SYNTAX score.

Variables	High SS n=509	Low SS n=979	p value
Age, years	59.7±10.7	57.8±11.4	< 0.001
Male gender, n (%)	379 (74.5)	740 (75.6)	0.633
Smoking, n (%)	195 (38.3)	382 (39.0)	0.790
Diabetes mellitus, n (%)	124 (24.4)	194 (19.8)	0.042
Hypertension, n (%)	241 (47.3)	399 (40.8)	0.015
LVEF, %	46.9±8.5	50.0±7.9	< 0.001
cTnI, ng/mL	3.2 (1.8-12.1)	2.6 (1.4-10.0)	0.082
FBG, mg/dL	122.6±54.5	115.2±40.3	0.007
WBC, 10^3/mm^3	9.3 (7.1-10.1)	8.7 (7-10.8)	0.048
Neutrophil, 10^3/mm^3	6.3 (4.8-8.3)	5.1 (4.1-6.8)	< 0.001
Lymphocyte, 10^3/mm^3	2.1 (1.6-2.7)	2.3 (1.8-2.9)	< 0.001
Platelet, 10^3/mm^3	263.3±77.2	250.4±67.9	0.001
Hemoglobin, g/dL	13.9±1.7	14.4±1.4	< 0.001
Hematocrit, %	43.0±5.2	43.2±4.5	0.441
C-reactive protein, mg/L	12.3 (6.5-21.3)	5.6 (2.7-10.4)	< 0.001
Albumin, g/dL	3.7±0.4	3.9±0.4	< 0.001
Creatinine, mg/dL	1.0±0.3	0.9±0.3	0.001
Total cholesterol, mg/dL	197.1±121.5	190.0±41.1	0.200
LDL- cholesterol, mg/dL	124.2±41.9	120.7±36.3	0.112
HDL- cholesterol, mg/dL	38.8±10.4	41.0±12.8	0.001
Triglyceride, mg/dL	187 (127-257)	164.5 (119-216)	0.001
NLR	2.5 (1.8-4)	2.3 (1.6-3.4)	< 0.001
PLR	121 (93.3-168.2)	105 (81.4-144.7)	< 0.001
CAR	3.4 (1.6-6.1)	1.4 (0.7-2.7)	< 0.001
SII, $\times10^2$	6.3 (4.4-10.8)	5.5 (3.8-9.1)	< 0.001
MII-1	28 (15.1-58.5)	13.6 (6.3-25.8)	< 0.001
MII-2, $\times10^2$	14.6 (7.2-27.0)	6.1 (2.9-12.0)	< 0.001
MII-3, $\times10^2$	75.4 (38.7-15.5)	32.8 (14.4-67.9)	< 0.001

Numerical variables were shown as mean±standard deviation or median (min-max). Categorical variables were shown as number (%). Abbreviations: CAR, C-reactive protein to albumin ratio; CCB, calcium channel blocker; FBG, fasting plasma glucose; HDL, high density lipoprotein; IRA, infarct-related artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; LDL, low density lipoprotein; LVEF, left ventricular ejection fraction; MII, multi-inflammation index; NLR, neutrophil to lymphocyte ratio; OAD, oral antidiabetic drug; PLR, platelet to lymphocyte ratio; RAS, renin-angiotensin system; RCA, right coronary artery; SII, systemic immune-inflammation index; SDV, severely diseased vessels; SYNTAX, SYNergy between Percutaneous Coronary Intervention with TAXus and cardiac surgery; ST, stent thrombosis; WBC, white blood cell.

Table 4. Independent predictors of high SYNTAX score

Variables	OR (95% CI)	p value
Univariable Regression		
Age	1.02 (1.01-1.03)	0.002
Diabetes mellitus	1.30 (1.01-1.68)	0.043
Hypertension	1.31 (1.05-1.62)	0.015
LVEF	0.95 (0.94-0.97)	< 0.001
cTnI		
FBG	1.04 (1.01-1.09)	0.003
WBC	1.03 (1.01-1.08)	0.050
Hemoglobin	0.84 (0.78-0.90)	< 0.001
HDL-cholesterol	0.98 (0.97-0.99)	< 0.001
Triglyceride	1.02 (1.01-1.03)	< 0.001
NLR	1.07 (1.03-1.12)	0.001
PLR	1.05 (1.03-1.07)	< 0.001
SII, x102	1.03 (1.02-1.05)	< 0.001
CAR	1.42 (1.35-1.50)	< 0.001
MII-1	1.03 (1.01-1.05)	< 0.001
MII-2, $\times 10^2$	1.07 (1.05-1.09)	< 0.001
MII-3, $\times 10^2$	1.11 (1.09-1.13)	< 0.001
Model I Multivariable Regression		
Age	1.03 (1.01-1.05)	< 0.001
LVEF	0.96 (0.94-0.98)	< 0.001
cTnI		
HDL-C	0.97 (0.95-0.99)	< 0.001
SII, $\times 10^2$	1.05 (1.03-1.07)	< 0.001
CAR	1.43 (1.35-1.51)	< 0.001
	Nagelkerke R2=0.433. p< 0.001	
Model II Multivariable Regression		
Age	1.03 (1.01-1.05)	< 0.001
LVEF	0.96 (0.94-0.98)	< 0.001
HDL-C	0.97 (0.95-0.99)	< 0.001
cTnI	2.27 (1.50-3.45)	< 0.001
MII-3, $\times 10^2$	1.10 (1.08-1.13)	< 0.001
	Nagelkerke R2=0.522. p < 0.001	

Abbreviations: CAR, C-reactive protein to albumin ratio; CI, confidence interval, FBG, fasting plasma glucose; HDL, high density lipoprotein; LVEF, left ventricular ejection fraction; MII, multi-inflammation index; NLR, neutrophil to lymphocyte ratio; OR, odds ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune-inflammation index; WBC, white blood cell.

DISCUSSION

To our best knowledge, this is the first study to evaluate the prognostic role of MII in ACS patients. The main consequences are: 1) MII-3 was an independent marker of acute ST and improved the model predicting acute ST. 2) MII-3 had better diagnostic performance than other inflammatory markers in predicting acute ST. 3) MII-3 was an independent predictor of higher SYNTAX scores. 4) The threshold value of MII to predict acute ST was an important risk factor for in-hospital mortality.

ST, a catastrophic complication of percutaneous coronary stent implantation, can occur acutely (first 24 hours after stent placement), early (first month), late (first year), or very late (after one year) (16). Despite the advances in technology and procedural techniques, the emergence of new generation stents, and dual antiplatelet therapy strategies (DAPT), it still has a significant incidence (17). The pooled analysis of multicenter coronary stent clinical trials reported that more than 80.0% of ST cases occurred within two days of PCI (18). In addition to patient characteristics such as hronic kidney disease, comorbid inflammatory conditions, advanced age, decompensated heart failure and early discontinuation of DAPT, reduction in stent size, coronary dissection, post-PCI TIMI flow <3, clopidogrel resistance, and bifurcation lesions increase the risk of acute ST (16, 19). On the other hand, there is growing evidence that inflammation contributes to the development of acute ST (5, 6). Therefore, we excluded patients with the above risk factors that might affect the relationship between inflammation and acute ST.

The SYNTAX score, which is a guide for revascularization in coronary artery disease, is a prognostic indicator for CV events (20). It also offers predictive value in acute ST (21). The immune system generates an inflammatory response in acute cardiovascular events, and it plays a role in smooth muscle cell proliferation, endothelial regeneration, oxidative stress, and platelet activation (8). These mechanisms are involved in the pathogenesis of acute ST and restenosis, in addition to being associated with higher SYNTAX scores (22). It can be used as a guide in the early prognosis prediction since inflammatory parameters provide an essential predictive value in cardiovascular events, including acute ST. However, inflammatory parameters offer different predictive values in cardiovascular events (23) as demonstrated in the current study. Therefore, simple and easily obtained stronger signals are needed to evaluate inflammation. A combined index derived from inflammatory parameters may exhibit superior diagnostic performance than its components. Previous studies have shown that MII offers a stronger prognostic value over old and new indicators of inflammation, including CRP, NLR, PLR, SII, and CAR in different patient groups (11-13). However, it has not yet been investigated in ACS patients. In this study, we evaluated MII, which is suggested to be a more power indicator of inflammation.

Acute phase reactants or CAR had a significant association with high SYNTAX score and acute ST, consistent with previous limited studies (24-26). The potential mechanism by which these acute phase reactants accelerate the development of plaque and thrombosis is that an increased release of CPR in circulation triggers the complement system, inducing leukocyte activity, platelet aggregation, lipid accumulation, and apoptosis (27), and decreasing albumin levels negatively affect anti-platelet aggregation, anti-inflammatory, antioxidant or anticoagulant activity

and disruption of vascular integrity (28). However, the effect of acute phase reactants on leukocyte activation causes increased accumulation of macrophages (29). It is known that increased platelet reactivity significantly increases the risk of acute ST (30). Therefore, a combined index containing acute phase reactants and inflammatory immune cells may provide superior diagnostic performance.

There are rare studies evaluating the relationship between SII or CAR and ST in patients with CAD undergoing PCI (24, 31). Ocal et al. (31) reported that high SII levels were associated with ST and that SII was an independent predictor of in-hospital and long-term mortality. Akboga et al. (24) evaluated the predictors of acute ST in patients with ACS undergoing PCI, and they found that increased levels of SII and CAR were independent predictors. In their study, CAR levels were a stronger indicator than SII. The present findings both support and extend previous studies. Firstly, Model I regression analysis showed that CAR and SII were independent predictors of acute ST. Secondly, ROC curve analysis showed that SII and CAR levels exhibited better diagnostic performance than NLR and PLR. However, the diagnostic performance of CAR and SII was similar. The diagnostic performance of SII compared to NLR and PLR in acute ST has not been evaluated previously. Thirdly, Model 2 regression analysis improved the variance in explaining acute ST. In contrast, ROC curve analysis showed that MII-3 had better diagnostic performance than other inflammatory indices.

This study was also the first to evaluate the relationship between MII and in-hospital mortality in ACS patients. The rate of in-hospital mortality in the acute ST group was consistent with the higher cumulative mortality rate reported in previous studies (2-4). The cut-off value of MII-3 for predicting acute ST was associated with a higher risk of mortality. Previous studies in patients with metastatic colorectal cancer and critically ill have shown that MII from leukocyte and CRP levels is an independent predictor of mortality and has better diagnostic performance than other markers of inflammation (11, 12). In addition, MII exhibited strong diagnostic performance in distinguishing between massive and non-massive pulmonary embolism patients (13). Considering the predictive and diagnostic performance value of MII in different patient groups, especially MII-3, it may be an essential prognostic screening tool in ACS patients.

Although this study had a prominent sample representative of the ACS cohort, its single-center, and retrospective design was the main limitation. Second, intravascular imaging techniques were not used to assess stent apposition or expansion. Third, early ST, late ST or very late ST evaluation was not performed. Finally, the levels of microRNA and cytokines that play a role in inflammation were not examined. These could better explain the contribution of inflammation in the development of acute ST.

CONCLUSION

MII-3, a powerful new indicator of inflammation, is a simple, inexpensive, and practical biomarker in predicting both high SYNTAX score, acute ST and in-hospital mortality in ACS patients. Moreover, MII-3 exhibited higher diagnostic performance than other inflammatory parameters. Therefore, it may be an essential prognostic screening tool for identifying high-risk patients prior to procedure in ACS patients undergoing PCI.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Ethics Committee (Date: 30.11.2022, Decision No: E1-22-3056).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: No conflict of interest was declared by the authors.

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